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Aspirin in the Treatment and Prevention of Cardiovascular Disease: Past and Current Perspectives and Future Directions

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ABSTRACT

In secondary prevention among a wide range of patients who have survived a prior occlusive vascular event, as well as during acute myocardial infarction and acute occlusive stroke, aspirin produces statistically significant and clinically important reductions in the risk of subsequent myocardial infarction, stroke, and vascular death. In primary prevention, aspirin reduces risk of a first myocardial infarction, but the data on stroke and vascular deaths remain inconclusive. In addition, the average absolute risk of subjects randomized in the primary prevention trials was so low that it is not possible to get reliable estimates of the benefit-to-risk ratio in primary prevention in subjects at moderate risk. Until the results of ongoing trials are available, nobody would disagree that a nonfatal myocardial infarction or stroke is more likely to be disabling than a nonfatal bleed. Thus, in primary prevention at present, the appropriate and judicious use of aspirin by clinicians based on individual clinical judgments that weigh their absolute benefits against the absolute risks of the drug, will avoid premature morbidity and possibly, mortality.

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As has been the case with aspirin in the treatment and prevention of cardiovascular disease, advances in medical knowledge proceed on several fronts, optimally simultaneously.[1,2] Basic researchers working in laboratories address the crucial question of why aspirin may have a role in the treatment and prevention of cardiovascular disease. Clinical investigators test the relevance of basic research findings concerning therapeutic interventions in their individual patients and preventive interventions in apparently healthy subjects. Epidemiologists and biostatisticians, optimally in collaboration with clinicians, formulate hypotheses from their descriptive studies and test hypotheses in analytic studies designed a priori to do so. Analytic studies, which include case-control and cohort designs, may be observational. In studies designed a priori to do so, both are useful to test moderate to large effects. For small to moderate effects, the amount of uncontrolled and uncontrollable confounding inherent in observational studies, no matter how large or well designed, are about as big as the effect sizes being sought. Thus, for small to moderate effects, especially of 50% or less, large-scale randomized trials designed a priori to test the hypothesis represent far and away the most reliable design strategy.[3] All these epidemiologic study designs address an equally crucial but complementary question of whether aspirin may have a role in the treatment and prevention of cardiovascular disease. Clinicians provide enormous benefits to their patients by their applications of advances in diagnosis and treatment. They also formulate

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many hypotheses from their broad clinical experiences, which include their case reports and case series. All these disciplines and every design strategy within a discipline provide importantly relevant and complementary information to a totality of evidence. When the totality of evidence is incomplete, it is appropriate to remain uncertain. When the totality of evidence is complete, health care providers can make the most rational clinical decisions for their individual patients, and policymakers can make the most rational decisions for the health of the general public.[1-3]

CLINICAL SIGNIFICANCE

- In secondary prevention, aspirin should be used among a very wide range of patients who have survived a prior occlusive vascular event, as well as during acute myocardial infarction and acute occlusive stroke.
- In primary prevention, aspirin should be prescribed by clinicians based on individual clinical judgments that weigh their absolute benefits on reducing the risk of a first myocardial infarction against the absolute risks of the drug.

BASIC RESEARCH

In some sense, aspirin is as old as medicine itself. In the 5th century BC, Hippocrates, the ancient Greek physician considered to be the father of medicine, found that an extract produced by the bark of the white willow tree (*Salix alba*) relieved aches and pains of his patients, particularly women in labor. Later this extract was found to contain salicin, a relative of acetyl salicylic acid, or aspirin. In 1897, Felix Hoffman, a chemist working in the laboratory of Friedrich Bayer in Elberfeld, Germany, first synthesized aspirin. He was motivated, in part, by his humanitarian wish to discover an effective and tolerable pain reliever for his father, who suffered from painful and disabling inflammatory arthritis. Aspirin became the most widely used drug in the 20th century, but it was not until 1971 that a plausible mechanism was proposed to explain why it might have a role in the treatment and prevention of cardiovascular disease.[4] Sir John Vane, working in the Wellcome Laboratories in London, England, UK, found that in platelets, small amounts of aspirin irreversibly acetylate the active site of cyclooxygenase required for the production of thromboxane A2, a powerful promoter of aggregation.[5] Vane was awarded the Nobel Prize in Medicine in 1982. Vane also hypothesized that higher doses would provide no greater benefit, and that far higher doses might even reverse the tendency due to the activation of reversible enzymes in the vessel wall. Nonetheless, the clinical relevance of prostacyclin sparing has never been demonstrated in randomized trials in humans.[4]

DESCRIPTIVE STUDIES

In 1950, Lawrence Craven, a general practitioner, formulated the hypothesis that aspirin prevents myocardial infarction. He noted that aspirin prolonged prothrombin time and mentioned reports of more frequent hemorrhaging among patients who chewed aspirin gum after a tonsillectomy or a tooth extraction. In his own case series he prescribed daily aspirin to 400 patients and noted over the next 2 years that none suffered a myocardial infarction.[6]

OBSERVATIONAL EPIDEMIOLOGIC STUDIES

Not surprisingly, some but not all case-control and cohort studies suggested that individuals who self-selected for use of aspirin had lowered risks of cardiovascular disease.[7-11] All these considerations suggested the need for large-scale randomized evidence, which was first obtained in the treatment or secondary prevention of cardiovascular disease.

ASPIRIN IN SECONDARY PREVENTION

The Antithrombotic Trialist's Collaboration performed the most comprehensive, worldwide meta-analysis of 195 randomized trials of antiplatelet therapy, principally with aspirin, among more than 135,000 high-risk patients with prior evidence of cardiovascular disease, including prior or acute myocardial infarction, prior or acute stroke or transient ischemia attacks, and other high-risk groups such as those with unstable angina, chronic stable coronary disease, and peripheral artery disease, as well as patients with coronary artery bypass grafts, or percutaneous coronary interventions.[12] Aspirin produced a statistically significant and clinically important 22% reduction in risk of subsequent vascular events. In this wide range of patients with prior cardiovascular disease, there were absolute reductions of approximately 36 vascular events per 1000 patients with a prior myocardial infarction treated for a mean of 27 months; 36 events per 1000 patients with a previous stroke or transient ischemic attack treated for 29 months; and 22 events per 1000 patients with other high-risk conditions treated for 22 months. With respect to dose of aspirin, in indirect comparisons as well as direct comparisons in 3 trials testing this hypothesis, there were no significant differences in efficacy or safety between doses of 75-150 mg/day and 160-325 mg/day.

ASPIRIN IN ACUTE MYOCARDIAL INFARCTION

The Second International Study of Infarct Survival (ISIS-2) randomized 17,187 patients within 24 hours on onset of their symptoms of acute myocardial infarction in a 2×2 factorial design to aspirin (162.5 mg), streptokinase (SK) (1.5 million units), both active treatments, or both placebos.[13] At 35 days, the primary prespecified end points of total mortality were reduced 23% by aspirin, 25% by SK, and 42% by aspirin and SK together. For aspirin, the mor-

tality benefits were similar regardless of whether administration was within 1 hour or up to 24 hours after onset of symptoms of acute myocardial infarction. In contrast, those treated within 6 hours with SK had a 30% reduction in mortality, and with SK and aspirin, a 52% reduction.

Among those assigned at random to aspirin there were statistically significant and clinically important reductions in vascular deaths of 23%, nonfatal reinfarction of 49%, and nonfatal stroke of 46%. Major bleeds requiring transfusions were similar in the aspirin and placebo groups (0.4%). After 35 days of treatment with aspirin there were no excess risks of cerebral hemorrhages and only a slight increase in major bleeds. In terms of absolute risk reductions of vascular events, there was an avoidance of 38 events per 1000 patients with an acute myocardial infarction treated for 1 month.

With respect to the benefit-to-risk ratio for aspirin given within 24 hours of onset of symptoms of acute myocardial infarction, 23 deaths were avoided, with no increase in cerebral hemorrhage. In contrast, SK given within 12 hours avoided 30 deaths, but caused 3 cerebral hemorrhages. As regards benefit to cost, the cost per life saved during acute myocardial infarction is about $88,000 for tissue plasminogen activator, $12,000 for SK, and $13 for aspirin.[14]

Thus, for all patients suffering acute myocardial infarction, aspirin should be administered promptly and continued long term.[15]

ASPIRIN IN ACUTE OCCLUSIVE STROKE

There are 2 landmark trials of aspirin in acute occlusive stroke. In each trial, occlusive stroke was initially diagnosed by the responsible clinician and subsequently confirmed by computed tomography scanning. The International Stroke Trial randomized 19,435 patients to 300 mg aspirin daily or open control.[16] The Chinese Acute Stroke Trial randomized about 20,000 patients to 160 mg aspirin daily or placebo.[17] Each showed benefits, and a meta-analysis showed a statistically significant and clinically important 11% reduction in vascular events as well as nonfatal stroke and vascular deaths. In terms of absolute risk reductions, for every 1000 patients with acute occlusive stroke, treatment with aspirin avoided 9 vascular events. Thus, for all patients with acute occlusive stroke, aspirin should be administered promptly and continued long term.[15]

ASPIRIN IN PRIMARY PREVENTION

The Physician's Health Study was the first to demonstrate a statistically significant benefit of aspirin on first myocardial infarction in 22,071 apparently healthy men.[18,19] Since that time, there have been 5 additional major trials in men and women that comprise over 90,000 subjects. A comprehensive meta-analysis of these 6 major primary prevention trials using individual participant data provided more reliable comparison of the benefits and risks of aspirin in apparently healthy people. While all 4 of the proportional reductions in major coronary events and in ischemic stroke in the primary and in the secondary prevention trials were similar to each other, vascular mortality was not reduced significantly in the primary prevention trials. Because the numbers of fatal events were far smaller in the primary prevention trials, a proportional reduction comparable with that in the secondary prevention trials could not be excluded. Regardless of the similarities in proportional reductions, the absolute benefits of aspirin are far smaller in the primary than in the secondary prevention trials due to the far lower absolute risks of the apparently healthy subjects.[20] In addition, a recently reported meta-analysis of randomized trials, most of which were not designed a priori to test the hypothesis, suggest beneficial effects of aspirin on overall cancer mortality.[21] Thus, the randomized data on prevention and treatment of colon polyps, as well as primary prevention of colon cancer, are more reliable than the data from other shorter-term trials which, in turn, are more reliable than the observational data on other cancers.

In the primary prevention trials, there were no significant modifications of the benefits of aspirin by age, smoking history, blood pressure, total cholesterol, body mass index, history of diabetes, or sex. In addition, an earlier suggestion that the beneficial effects of aspirin in primary prevention might differ between men and women has not been supported by the more robust data from the secondary prevention trials.[22] Finally, it has been hypothesized that a dose of at least 162.5 mg daily may be necessary to observe beneficial effects of aspirin for the primary prevention of stroke and myocardial infarction.[23]

Four trials involving intermediate-risk individuals are ongoing and might yield more-reliable evidence on the balance of benefits and risks of aspirin in apparently healthy subjects at moderate risk. In each of these trials of aspirin in the primary prevention of cardiovascular disease, a slightly different strategy has been adopted to identify individuals at intermediate risk. The Aspirin to Reduce Risk of Initial Vascular Events (ARRIVE) study is a large-scale, randomized, double-blind, placebo-controlled trial in which investigators have enrolled over 12,000 men and women with a predicted risk of a first coronary event of 1.5% per year using a modification of the Framingham Risk Score.[24] Researchers in the Aspirin in Reducing Events in the Elderly (ASPREE) trial are enrolling elderly individuals aged $\geq$70 years considered to be at intermediate risk.[25] In both trials, A Study of Cardiovascular Events in Diabetes (ASCEND)[26] and the Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trials in Diabetes (ACCEPT-D),[27] intermediate risk is defined as individuals with diabetes mellitus but no known vascular disease. High levels of adherence and follow-up as well as accrual of sufficient numbers of cardiovascular disease end points are necessary in all these ongoing trials to provide reliable evidence about the absolute benefits and risks of aspirin for primary prevention in various groups of individuals at intermediate cardiovascular risk.

Until the results of these trials are published, judgments about prescribing long-term aspirin therapy for apparently healthy individuals at intermediate cardiovascular risk should continue to be made on a case-by-case basis and are

best informed by the available meta-analyses of the large-scale individual trials designed a priori to test aspirin for primary prevention. General guidelines that advocate the routine use of aspirin in all apparently healthy individuals do not seem to be justified. The increasing burden of cardiovascular disease in developed and developing countries underscores the need for the more-widespread use of drug therapies of proven net benefit in the primary prevention of cardiovascular disease, such as statins to lower low-density-lipoprotein cholesterol levels, and various drugs to lower blood pressure.[28,29]

NEW AND NOVEL MECHANISMS OF ASPIRIN

While atherosclerosis is the principal underlying cause of cardiovascular disease, in the vast majority of cases the proximate cause is thrombosis.[15] Even 41 years after Vane's landmark findings, the most plausible biological mechanism of action of aspirin in the reduction of risks of occlusive vascular events in a very wide range of patients is derived from its ability in platelets to irreversibly acetylate the active site of cyclooxygenase required for the production of thromboxane A2, a powerful promoter of aggregation.[5] This antiplatelet property of aspirin to irreversibly inhibit platelet-dependent cyclooxygenase is sufficient to explain the statistically significant and clinically important beneficial effects on occlusive vascular diseases in secondary prevention and on a first myocardial infarction in primary prevention.

Nonetheless, basic research has suggested possible mechanisms by which aspirin may have additional beneficial effects mediated through nitric oxide (NO) formation.[30] Nitric oxide is produced via 2-step oxidation of the amino acid L-arginine. Nitric oxide (NO) inhibits platelet aggregation, neutrophil adhesion to endothelial cells, and expression of inflammatory molecules. In high concentrations, NO inhibits the proliferation of smooth muscle cells.[31] More specifically, NO is released from vascular endothelium and plays a crucial role in the maintenance of vascular homeostasis. In basic research, endothelial NO synthase (NOS) appeared to be a novel and functionally relevant target of aspirin, using the direct guanylyl cyclase activator 3-(50-hydroxymethyl-20-furyl)-1-benzylindazole (YC-1) or rat fetal lung fibroblast cell line (RFL-6) reporter cells that are devoid of any NOS activity.[6] In a cell culture model of oxidant injury, aspirin-dependent NO formation increased endothelial protection. In addition, in platelets, aspirin acetylates NO synthase. Thus, in endothelial cells and possibly platelets, aspirin is capable of activating the NO cyclic guanosine monophosphate signaling pathway.[32,33] Finally, in the endothelium, NO and cyclic guanosine monophosphate produce antioxidant protection and improved integrity.[34] Heme oxygenase is a cytoprotective downstream target and is considered a surrogate for biologically active NO.[10] Asymmetric dimethyl arginine is a competitive inhibitor of NOS.[35,36] In the first 2 randomized trials in humans, willing and eligible participants were randomized to each of 5 clinically relevant doses of aspirin of 81 mg, 325 mg, 650 mg, and 1200 mg daily for 12 weeks. All doses of aspirin increased NO formation as measured by heme oxygenase and asymmetric dimethyl arginine after 12 weeks of treatment and follow-up. The first trial consisted of high-risk primary prevention subjects with metabolic syndrome,[37] and the second randomized patients with chronic stable coronary disease.[38] Thus, basic research suggested additional plausible mechanisms by which aspirin may have additional beneficial effects, and 2 randomized short-term trials on markers of NO formation showed beneficial effects of aspirin. The current totality of evidence in humans supports the need for further research, including direct randomized trials of the 2 most widely used doses of aspirin, 81 mg and 325 mg, to allow the first direct comparisons on progression of atherosclerosis after 2 years.

CONCLUSIONS

In secondary prevention among a wide range of patients who have survived a prior occlusive vascular event, as well as during acute myocardial infarction and acute occlusive stroke, aspirin produces statistically significant and clinically important reductions in the risk of subsequent myocardial infarction, stroke, and vascular death. In addition, the most plausible mechanisms of aspirin are on thrombosis, and statins on atherosclerosis, suggesting that the benefits of both drugs used simultaneously would be additive.[39] Importantly, relevant information on this hypothesis was generated from a meta-analysis of randomized trials of statins in secondary prevention, in which aspirin was used in varying frequencies. In this meta-analysis, the combination of aspirin and statins conferred, at the very least, additive clinical benefits than either agent alone on myocardial infarction, occlusive stroke, and death from cardiovascular disease. In fact, the probability that the benefits were greater than just additive was 92%. Finally, these benefits were apparent in the 2 largest individual trials, namely Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) and Cholesterol And Recurrent Events (CARE), that comprised this meta-analysis.[40] When aspirin is given promptly during acute myocardial infarction and continued for 30 days, there are statistically significant and clinically important reductions in subsequent myocardial infarction, stroke, and vascular death. Thus, the more widespread and routine use of aspirin in secondary prevention and during acute myocardial infarction will avoid premature morbidity and mortality.

In primary prevention, aspirin reduces risk of a first myocardial infarction, but the data on stroke and vascular deaths remain inconclusive. In addition, the average absolute risk of subjects randomized in the primary prevention trials was so low that it is not possible to get reliable estimates of the benefit-to-risk ratio in primary prevention in subjects at moderate risk. Nonetheless, to maximize the benefit-to-risk ratio in primary prevention, most current guidelines recommend that aspirin be given to those above

a certain level of absolute risk at baseline. These guidelines implicitly assume, perhaps erroneously, that risks of bleeding remain constant. While the currently available trial results could well help inform appropriate individual clinical judgments of use of long-term aspirin, they do not seem to justify general guidelines advocating the routine use of aspirin in all apparently healthy individuals above a moderate level of risk of coronary heart disease. The ongoing trials in moderate- to high-risk primary prevention may facilitate a reliable benefit-to-risk ratio of aspirin in primary prevention among subjects at moderate risk.[20] Nobody would disagree that a nonfatal myocardial infarction or stroke is more likely to be disabling than a nonfatal bleed, but any judgment about the use of aspirin in primary prevention should be made on an individual clinical basis. Thus, in primary prevention, at present, the appropriate and judicious use of aspirin by clinicians based on individual clinical judgments that weigh the absolute benefits on first myocardial infarction against the absolute risks of the drug, will avoid premature morbidity and possibly, mortality, from cardiovascular disease.

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